UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,345	07/14/2006	Johannes Reinmuller	WEICKM-0061	2694

23599 7590 10/24/2008

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
10/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,345	REINMULLER ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *7,8,10 and 15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *14 July 2006 and 5 September 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed on 23 September 2008, in which claims 1-21 were currently amended, is acknowledged.

Claims 1-21 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/EP2005/000215 filed on 12 January 2005 and claims priority to Germany foreign application 10 2004 002 001.9 filed on 14 January 2004. A certified copy of the foreign priority document in German has been received. No English translation has been received.

Information Disclosure Statement

The information disclosure statements (IDS) dated 14 July 2006 and 5 September 2006 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, unless otherwise noted. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

References 006, 007, 008 and 009 on the IDS dated 14 July 2006 were not considered because copies of the documents were not provided to the Office.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-13, drawn to a method of using hyaluronic acid in crosslinked form for treating inflammatory skin or mucous

membrane diseases, in the reply filed on 23 September 2008 is acknowledged. The traversal is on the ground(s) that the Gallina (U.S. Patent No. 5,679,655) reference used to show that the inventions of Groups I-IV are not linked by a common inventive concept in the sense of rule 13.1 PCT is untenable because Gallina teaches only the use of hyaluronic acid, and not hyaluronic acid in the crosslinked form. This is found persuasive because the common inventive concept of the independent claims of each group do involve hyaluronic acid in the crosslinked form. In view of this argument, Examiner withdraws the Gallina reference. With respect to hyaluronic acid in the crosslinked form as the common technical feature, U.S. Patent No. 7,716,224 to Sakurai *et al.* teaches crosslinked hyaluronic acid which can exert various useful properties (column 1, lines 66-68).

As a result, no special technical features exist among the different groups because the inventions in different Groups fail to make a contribution over the prior art with respect to novelty and inventive step. In conclusion, there is a lack of unity of inventions, and therefore restriction for examination purposes as indicated is proper.

In view of Applicants' amendment of claims 1-13, originally reciting “The use of” in the preamble of the claims filed on 14 July 2006, to “A method for” in the preamble of the claims filed on 23 September 2008, the Restriction Requirement has been amended as follows: The claims of Group II, claim 14, drawn to a process for treating an inflammatory skin or mucous membrane disease, will be rejoined with the claims of Group I.

Applicants further argue that undue burden has not been established. The inventions of Group I/II, Group III and Group IV relate to methods of treating various conditions and/or diseases. As such, different fields of search would be required. For example, Group III relates to an inflammatory disease of the eye while Group IV relates to treatment of skin or soft tissue defects. A search for methods of treating inflammatory disease of the eye would not yield results for methods of treating skin or soft tissue defects. As such, there is undue burden in examining the full scope of the claimed inventions, and restriction is proper.

The Applicants further elect the absence of an inhibitor of hyaluronic acid degradation in the composition, the absence of another glycosaminoglycan in the composition, and viral skin diseases which lead to wart formation as the inflammatory skin or mucous membrane disease.

The requirement is deemed proper and is therefore made FINAL.

Claims 15-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 7, 8 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-6, 9 and 11-14 will be examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating specific inflammatory skin or mucous membrane diseases, comprising administering to a subject in need thereof an effective amount of hyaluronic acid in crosslinked form, does not reasonably provide enablement for preventing the same method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a method of preventing an inflammatory skin or mucous membrane disease by administering an effective amount of hyaluronic acid in crosslinked form.

Relative skill of those in the art: The relative skill of those in the art is high.

Breadth of claims: The scope of the claims specifically include a method for preventing an inflammatory skin or mucous membrane disease in said subject

State of the prior art/Predictability or unpredictability of the art: According to the Merriam-Webster Online dictionary (PTO-892, Ref. U), prevent is defined as "to keep from happening or existing". There is no prior art disclosing the prevention of an inflammatory skin or mucous membrane disease.

Furthermore, Stedman's Medical Dictionary online teaches that inflammation is "[a] fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including: 1) the local reactions and resulting morphologic changes, 2) the destruction or removal of the injurious material, [and] 3) the responses that lead to repair and healing" (PTO-892, Ref. V) Thus, a skilled artisan would view that inflammation of the skin can be caused by many different factors, including bacterial or viral infections, environmental influences, or self or foreign immunity, in the case of autoimmune diseases. For example, psoriasis is generally viewed as an autoimmune disease, viral skin disease which leads to wart formation is caused by viruses and inflammatory intestinal diseases are generally caused by bacteria, but can also be

caused by viruses. Therefore, since inflammatory skin or mucous membrane diseases arise from many factors, including genetic, immunoinflammatory and environmental factors, a skilled artisan would view a method of preventing such a disease as highly unlikely because no one method can be a cure for all factors, particularly when involving unknown environmental factors.

Amount of guidance/Existence of working examples: There are **no** working examples present which show that inflammatory skin or mucous membrane disease in a subject can be prevented. The working examples in the specification merely provide data showing the effect of crosslinked hyaluronic acid in treating patients suffering from atopic dermatitis and viral warts. No examples are provided to show the prevention of the onset an inflammatory skin or mucous membrane disease.

Lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the use of the claimed compounds for preventing weight gain in a subject as recited in the instant claims.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., the amount of guidance provided, the predictability of the art and the lack of working examples, to

practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 1-6, 9 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some particular inflammatory skin or mucous membrane diseases, such as atopic dermatitis and some viral warts by administering an effective amount of hyaluronic acid in crosslinked form, does not reasonably provide enablement for treating any inflammatory skin or mucous membrane diseases by administering an effective amount of hyaluronic acid in crosslinked form. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a method of treating an inflammatory skin or mucous membrane disease by administering an effective amount of hyaluronic acid in crosslinked form.

Relative skill of those in the art: The relative skill of those in the art is high.

Breadth of claims: The claims are extremely broad in that they encompass the treatment of any inflammatory skin or mucous membrane disease.

Amount of guidance/Existence of working examples: The specification only provides working examples for treating atopic dermatitis and viral warts by administering to a subject crosslinked hyaluronic acid. The specification **does not** provide any working examples for any other inflammatory skin or mucous membrane disease, such as seborrheic or microbial eczema, pruritus, red lichen, or acne conglobata.

Lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP § 2164.

State of the prior art/Predictability or unpredictability of the art: The skilled artisan would view that the treatment of all inflammatory skin or mucous membrane diseases using one composition is highly unlikely. As discussed above, Stedman's Medical Dictionary online teaches that inflammation is "[a] fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including: 1) the local reactions and resulting morphologic changes, 2) the destruction or removal of the injurious material, [and] 3) the responses that lead to repair and healing" (PTO-892, Ref.

V) Thus, a skilled artisan would view that inflammation of the skin can be caused by many different factors, including bacterial or viral infections, environmental influences, or self or foreign immunity, in the case of autoimmune diseases. For example, psoriasis is generally viewed as an autoimmune disease, viral skin disease which leads to wart formation is caused by viruses and inflammatory intestinal diseases are generally caused by bacteria, but may also be caused by viruses. Leshchinskii *et al.* (PTO-892, Ref. W) teach that the anti-inflammatory activity of drugs is usually investigated on various models of inflammation because certain drugs exhibit anti-inflammatory effect on some models but not on others (p. 384, paragraph 2). This is likely because of the differences in the action of the factors producing the inflammation. Thus, it makes it necessary to study the pathogenesis of different types of inflammation, and also the mechanism of action of drugs with the anti-inflammatory activity.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize, or recognize, the identity of the members of the genus by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co*. Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of ordinary skill in the art would be unable to fully predict possible physiological activities of any

compounds having claimed functional properties in the pharmaceutical compositions herein.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of making the claimed composition as recited in the instant claims.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., breadth of claims, the amount of guidance provided and in particular, the predictability of the art, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1-4, 9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.* (herein referred to as the '322 patent, PTO-892, Ref. A) in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (herein referred to as the '224 patent, PTO-892, Ref. B).

The Falk '322 patent discloses that a therapeutically effective amount of hyaluronic acid in a composition is useful in the treatment of skin diseases and conditions by topically administering said composition to a subject. The topical composition may be used to treat diseases and conditions of the skin such as genital warts cervical cancer, human papilloma virus (HPV), and psoriasis, among others (column 7, lines 10-22; column 12, lines 28-39). The composition may be in any

suitable form, such as a lotion or a cream (column 8, lines 61-62). As shown in Formulation (A), the weight of sodium hyaluronate is 661,600 (661 kDa) (column 13, lines 10-23). Examples 1-7 illustrate the use of the composition on human patients with lesions (Examples 1-3) or psoriasis (Example 7) (columns 25 and 26).

The Falk '322 patent does not explicitly teach that hyaluronic acid is in the crosslinked form used in a method of treating an inflammatory skin or mucous membrane diseases. It is noted that the Falk '322 patent does not explicitly teach the degree of crosslinking as instantly claimed.

The Sakurai '224 patent teaches that the hyaluronic acid typically administered to a subject is isolated and purified from a source and lacks the stringiness and viscoelasticity of hyaluronic acid typically found in the living body (column 1, lines 35-40). Moreover, hyaluronic acid is known to undergo enzymatic decomposition or non-enzymatic oxidation-reduction decomposition after being administered to a living body, especially at diseased sites (column 1, lines 41-44). Crosslinked hyaluronic acid, on the other hand, shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, crosslinked hyaluronic acid has a wide variety of medical and cosmetic uses (column 1, lines 61-63). The crosslinking index (percent of crosslinking) of the resultant crosslinked hyaluronic acid or salt thereof from a reaction, may be controlled by varying the molar ratio of the hyarluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). The crosslinked hyaluronic acid may be used in skin cosmetics (column 4, lines 4-6), for application on, for example, shaving, cracking, and chappy skin (column 4, lines

28-30). The cosmetic containing crosslinked hyaluronic acid may be in the form of a cream, lotion, or hair cosmetic (column 4, lines 30-33). Example 8 illustrates the use of crosslinked hyaluronic acid on rabbits (column 10, lines 14-68).

The Sakurai '224 patent does disclose crosslinked hyaluronic acid with varying degrees of crosslinking, as indicated by their crosslinking index. For example, crosslinked hyaluronic acids with a crosslinking index per 1000 repeating disaccharides in hyaluronic acid of 8.5, 7.5, 13 and 40 and disclosed in Examples 1-4, respectively. Moreover, the Sakurai '224 patent teaches that the degree of crosslinking may be controlled by varying the molar ratio of the hyarluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). Thus, it is considered that one of ordinary skill in the art would have the capabilities of adjusting their reaction to obtain a crosslinked hyaluronic acid with the desired percent of crosslinking.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Falk '322 patent, concerning the treatment of skin diseases and conditions by administering a composition comprising a therapeutically effective amount of a non-toxic drug that inhibits prostaglandin synthesis with a therapeutically effective amount of hyaluronic acid, with the teachings of the Sakurai '224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition. One would have been motivated to combine the teachings in order to receive the expected benefit, as

suggested in the Sakurai '224 patent, that crosslinked hyaluronic acid shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, one of ordinary skill in the art would know that the compound's half-life would be increased as it is no longer subjected to enzymatic and non-enzymatic oxidation-reduction decomposition.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.* (herein referred to as the '322 patent, PTO-892, Ref. A) in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (herein referred to as the '224 patent, PTO-892, Ref. B) as applied to claims 1-4, 9 and 11-14, and further in view of chapter publication by Wilkinson (PTO-892, Ref. X).

The teachings of the Falk '322 patent and the Sakurai '224 patent were as disclosed above in section [0001] of the claim rejections under 35 USC § 103.

The references do not teach a method wherein the composition comprises hyaluronic acid in both crosslinked and uncrosslinked form.

Wilkinson teaches the physiochemical factors involved in the transfer of drugs across membranes. Figure 1-6 discloses the therapeutic window in which a drug shows effectiveness (p. 25, first column). This window varies depending on factors such as the dosage, toxicity, absorption, distribution and its elimination half-life (p. 25, first column,

first incomplete paragraph; p. 26, second column, first incomplete paragraph). In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion so as to maintain a steady-state concentration of drug associated with the therapeutic window (p. 26, first column, subheading "Maintenance Dose", first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Falk '322 patent, concerning the treatment of skin diseases and conditions by administering a composition comprising a therapeutically effective amount of a non-toxic drug that inhibits prostaglandin synthesis with a therapeutically effective amount of hyaluronic acid, with the teachings of the Sakurai '224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition, with the teachings of Wilkinson, regarding the therapeutic window of a drug and how it varies according to the drug's absorption, distribution and elimination characteristics. Since the Falk '322 patent teaches the treatment of skin diseases and conditions by administering a prostagladin synthesis inhibitor along with hyaluronic acid and the Sakurai '224 patent teaches that crosslinked hyaluronic acid is resistant to enzymatic and chemical degradation, as well as the use of crosslinked hyaluronic acid in cosmetics for application to the skin, then one would have been motivated to combine the teachings to make a composition comprising hyaluronic acid in both crosslinked and uncrosslinked form, in order to receive the expected benefit, that the combined composition would

increase the therapeutic window of the drug. One of ordinary skill in the art would know that the uncrosslinked compound likely takes effect faster, but is also degraded faster, while crosslinked hyaluronic acid would remain in the bloodstream longer, thereby increasing the therapeutic window of effectiveness of the drug.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623